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A short enantioselective synthesis of (*R*)-nostrenol

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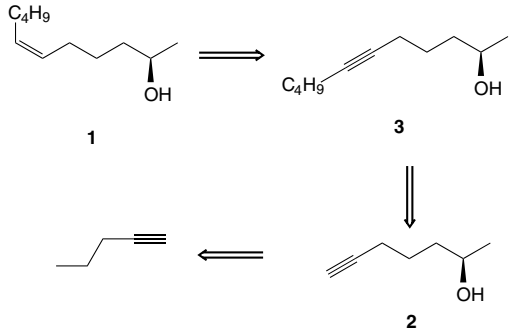
Abstract—The catalytic asymmetric synthesis of (−)-(*R*)-nostrenol is described in five steps starting from commercially available 1-pentyne. The key steps are a Noyori catalytic and asymmetric hydrogen transfer and a Cp_2TiCl_2 catalyzed hydroalumination.

1. Introduction

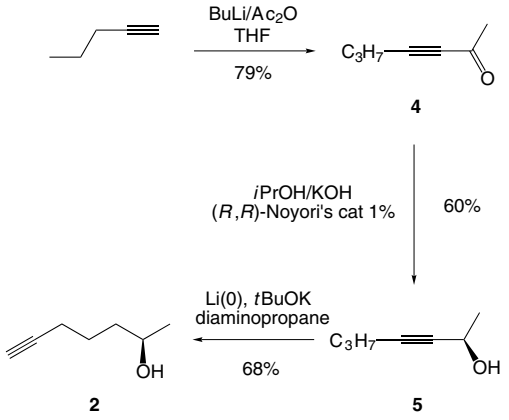
Insects semiochemicals, including pheromones and allelochemicals, play an important role in the chemical communications between organisms.[1,2] From a structural point of view, insect semiochemicals are usually constituted with an unsaturated/saturated hydrocarbon chain with some chiral branching (alkyl chain or oxygen functionality). (*R*)-Nostrenol [(−)-(*R*)-(*Z*)-undec-6-en-2-ol] **1** is the major semiochemical isolated from ant-lions (*Euroleon nostras* and *Grocus bore*).[3,4] We have recently developed a rapid access to chiral building block **2**,[5] and a Cp_2TiCl_2 catalyzed (*Z*)-selective reduction[6] of internal alkynes. In our retrosynthetic analysis, we sought to combine these two methodologies to develop a rapid and efficient access to (*R*)-nostrenol (Scheme 1).



Scheme 1.

2. Results and discussion

Starting from commercially available 1-pentyne, propargylic ketone **4** was obtained in 79% yield using butyl lithium and acetic anhydride (Scheme 2). Catalytic asymmetric hydrogen transfer, under Noyori's conditions,[7] led to the corresponding propargylic alcohol **5** in 60% yield. As previously described,[5] the enantiomeric excess was determined to be greater than 95% ee by ^{13}C and natural abundance deuterium (NAD) ^{2}D NMR spectroscopy in a chiral liquid crystal.[8] Finally a chiral building block **2** was obtained in 68% yield using a racemization-free[5] (determined by NAD^{2}D NMR) KAPA reaction.[9]



Scheme 2.

The free acetylenic compound was then alkylated with butyl iodide, in the presence of HMPA,[10] leading to desired alkyne **3** in 75% yield with $[\alpha]_D^{25} = -10.9$ (*c* 0.92,

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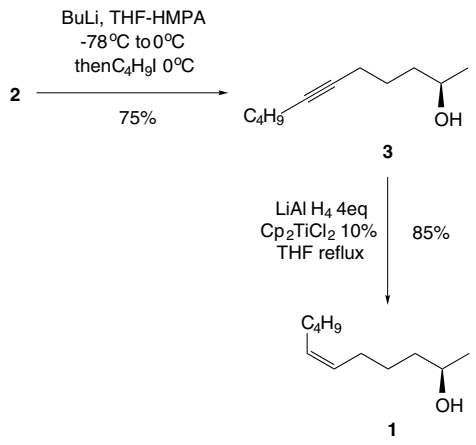
$CHCl_3$), which can be compared with the previously reported[4] value $[\alpha]_D^{23} = -8.0$ (*c* 0.84, $CHCl_3$) (Scheme 3).



Scheme 3.

The final reduction of the alkyne to the (*Z*)-alkene was carried out by using our previously reported[6] Cp_2TiCl_2 catalyzed hydroalumination. (−)-(*R*)-Nostrenol[11] was thus obtained in 85% yield with a (*Z*)-selectivity higher than 95% [determined by comparison (^{13}C NMR) with an (*E*)-sample obtained using the Rossi and Carpita methodology[12]].

3. Conclusion

In conclusion we have developed a short (five steps, 20% overall yield, from commercially available 1-pentyne) catalytic asymmetric total synthesis of the ant-lion semiochemical (−)-(*R*)-nostrenol, highlighting the versatility of **2** as a chiral building block and the efficiency of the Cp_2TiCl_2 catalyzed (*Z*)-selective reduction of internal alkynes.

4. Experimental

4.1. General methods

Unless otherwise specified, the reactions were carried out in oven-dried glassware under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, or at 250 and 63 MHz, in $CDCl_3$ as solvent: chemical shifts are given in ppm. Column chromatography was performed on silica-gel 230–400 mesh. THF was distilled from sodium/benzophenone. Optical rotations were determined operating at the sodium D line.

4.2. (*R*)-Hept-3-yn-2-ol, 5

In a flask containing (*R*,*R*)-tosyldiphenylethylendiamine (333 mg; 0.9 mmol; 1 mol%) and di-μ-chlorobis[(*p*-cymene)chlororuthenium(II)] (STREM, 275 mg; 0.45 mmol; 0.5 mol%) was added propan-2-ol (20 mL). The solution was degassed three times using the Schlenk procedure and warmed to 80 °C. After 1 h, the solution was cooled to room temperature and flame-dried potassium hydroxide (126 mg; 2.25 mmol; 2.5 mol%) added. The red solution then turned to purple. After 5 min, a solution of ketone **3** (10 g; 90.9 mmol) in propan-2-ol (480 mL) was added through a cannula. After stirring for 48 h under argon at room temperature, the solvent was removed under vacuum at room temperature and the residue purified (pentane/diethyl ether 9:1). The desired alcohol was obtained in 60% yield as a light yellow oil. TLC: SiO_2/(heptane/ethyl acetate 8:2) $R_f = 0.33$. ^1H NMR ($CDCl_3$ 300 MHz): 4.50 (qt, 6.5, 1.9, 1H); 2.16 (td, 7.0, 1.9, 2H); 1.95 (br, 1H); 1.51 (∼sext, 2H); 1.42 (d, 6.5, 3H); 0.96 (t, 7.0, 2H). ^{13}C NMR ($CDCl_3$ 75 MHz): 84.4; 82.4; 58.5; 24.7; 22.1; 20.5; 13.4. Rotation: lit.[13]: $[\alpha]_D^{25} = +14.8$ (*c* 0.662, $CHCl_3$; ee = 78%), Found: $[\alpha]_D^{25} = +30.7$ (*c* 1.01, $CHCl_3$; ee >95%). Data are in agreement with previously reported data.[13]

4.3. (*R*)-Hept-6-yn-2-ol, 2

According to the general procedure described by Abrams and Shaw,[9] in a flame dried tricol, and under argon, containing lithium (0.89 g; 130 mmol; 6 equiv) was added diaminopropane (distilled over BaO and stored over 4 Å MS) (80 mL). The solution was stirred for 30 min at room temperature and then at 70 °C for 4 h (until the total disappearance of the blue color). After cooling to room temperature, *t*BuOK (9.6 g; 84 mmol) was added to the reaction mixture and the resulting yellow solution stirred for a further 30 min. The propargylic alcohol **4** (2.4 g, 21.4 mmol) was then added dropwise. After stirring for 30 min, the reaction was poured into crushed ice/water (250 mL). The reaction mixture was then extracted with diethyl ether (four times, 125 mL). The combined organic layers were washed twice with 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, and the solvent removed under vacuum. Pure alcohol (1.63 g; 68%) was obtained after chromatography (pentane/diethylether 8:2). $R_f = 0.33$ Heptane/ethyl acetate 7:3. ^1H NMR ($CDCl_3$ 300 MHz): 3.83 (m, 1H); 2.23 (td, 6.7, 2.6, 2H); 1.96 (t, 2.6, 1H); 1.82 (br, 1H); 1.75–1.45 (m, 4H); 1.19 (d, 6.2, 3H). ^{13}C NMR ($CDCl_3$ 75 MHz): 84.2; 68.4; 67.5; 38.1; 24.6; 23.5; 18.3. Rotation: lit.[14]: $[\alpha]_D^{25} = -13.6$ (*c* 0.404, $CHCl_3$; ee >95%); found: $[\alpha]_D^{25} = -14.5$ (*c* 1.01, $CHCl_3$; ee >95%). Data are in agreement with the previously reported data.[14]

4.4. (*R*)-Undec-6-yn-2-ol, 3

To a solution of **2** (79 mg; 0.70 mmol) in THF (2 mL), at −78 °C and under argon, was added dropwise *n*-butyllithium (1.50 mL; 1.6 M solution in hexane; 2.40 mmol; 3.4 equiv). After 20 min, the temperature was allowed to warm up to 0 °C and HMPA (0.75 mL; 4.3 mmol; 6 equiv) added to the reaction mixture. A solution of 1-iodobutane (193 mg; 1.03 mmol; 1.5 equiv) in dry THF

(1 mL) was then added and the reaction mixture stirred overnight with the temperature being allowed to rise to the ambient. The reaction was quenched by the addition of 1 M HCl and the mixture poured into water (20 mL). It was then extracted with diethyl ether (4×15 mL) and the combined extracts washed with water and brine, dried over $MgSO_4$, and evaporated under vacuum. Chromatographic purification of the crude residue on silica (heptane/ethyl acetate 8:2) gave 90 mg (75%) of pure **3** as a light yellow oil. TLC: SiO_2/(heptane/ethyl acetate 7:3) $R_f = 0.35$; ^1H NMR ($CDCl_3$ 300 MHz): 3.84 (q, $J = 5.8$, 1H); 2.18–2.12 (m, 4H); 1.58–1.36 (m, 9H); 1.20 (d, $J = 6.4$, 3H); 0.90 (t, 3H, $J = 7.0$, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 80.7; 79.8; 67.7; 38.4; 31.2; 25.3; 23.5; 21.9; 18.7; 18.4; 13.6. Rotation: lit.[4b]: $[\alpha]_D^{25} = -8.0$ (*c* 0.84, $CHCl_3$; ee >95%); Found: $[\alpha]_D^{25} = -10.9$ (*c* 0.92, $CHCl_3$). Data are in agreement with the previously reported data.[4b]

4.5. (*R*)-Nostrenol, 1

To a suspension of $LiAlH_4$ (95 mg; 2.4 mmol; 4 equiv) in dry THF (3 mL) was added Cp_2TiCl_2 (15 mg; 0.06 mmol; 0.1 equiv). A solution of **3** (103 mg; 0.6 mmol; 1 equiv) in dry THF (3 mL) was then added and the mixture heated to reflux for 16 h. After cooling to rt, the mixture was diluted with diethyl ether and neutralized with 1 M HCl. The aqueous phase was extracted with diethyl ether and the combined organic extracts washed with 1 M HCl, saturated aqueous hydrogen carbonate and brine, dried over $MgSO_4$ and the solvent removed under vacuum. The crude residue was purified by column chromatography on silica (heptane/ethyl acetate 9:1 to 7:3) to give (*R*)-nostrenol (86 mg; 85%) as a light yellow oil. TLC: SiO_2/(heptane/ethyl acetate 7:3) $R_f = 0.43$; ^1H NMR ($CDCl_3$ 300 MHz): 5.37 (m, 2H); 3.81 (m, 1H); 2.05 (m, 4H); 1.48–1.27 (m, 9H); 1.20 (d, $J = 6.1$, 3H); 0.89 (t, $J = 7.0$, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz): 130.3; 129.3; 68.0; 38.9; 31.9; 27.1; 26.9; 25.9; 23.5; 22.3; 14.0. Rotation: lit.[4b]: $[\alpha]_D^{25} = -5.5$ (*c* 0.78, $CHCl_3$; ee >95%); found: $[\alpha]_D^{25} = -4.9$ (*c* 0.91, $CHCl_3$). Data are in agreement with the previously reported data.[4b]

Acknowledgements

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11. ^1H and ^{13}C NMR and $[\alpha]_D^{24}$ −4.9 (*c* 0.91, $CHCl_3$) are in agreement with the previously reported data[4b]: $[\alpha]_D^{23}$ −5.5 (*c* 0.78, $CHCl_3$).
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